Remarks

Claims 104-110 and 112-114 are currently pending and under examination. Claims 104 and 108 are currently amended for purposes of greater clarity only. No claims are canceled. No new matter has been introduced.

The examiner's withdrawal of the finality of the previous action due to new rejections and objections is acknowledged.

Claim Objections

The examiner objected to claims 107 and 108 as being of improper dependent form for failing to further limit the subject matter of a previous claim. The examiner particularly objects to the term "nucleotide analog or derivative" recited in claims 107 and 108. According to the examiner, "the term does not indicate whether the backbone or sequence is modified or any nucleotide can replace a nucleotide in the sequence and be considered an analog or derivative." The examiner further states, "the term could embrace an oligonucleotide that comprises a CG dinucleotide even though the claim from which they depend requires that the oligonucleotide does not comprise a CG dinucleotide."

Applicant respectfully disagrees. Applicant points out that, in addition to the fact the terms at issue are well defined and routinely used in the art, the phrase "a nucleotide analog or derivative" has been clearly defined in the specification. As set forth on page 8 of the original specification and on page 10 of the substitute specification filed on September 24, 2003, the phrase "a nucleotide analog or derivative" is described as follows:

> As used in accordance with the present invention, the term "nucleotide analog or derivative" denotes any nucleoside phosphate *the nucleoside of which* deviates in its chemical structure from the nucleosides guanosine, adenosine, thymidine, uridine or cytidine. Such modified nucleosides are well known to the person skilled in the art and comprise, e.g., 5,6-dihydrouridine, ribothymidine, inosine or 1-methylguanosine (see, e.g. Lewin B, Genes, 1983, John Wiley & Sons, Inc., NY). In accordance with the present invention, one or more nucleotides of the oligonucleotides of the present invention or the oligonucleotides to be employed

> in accordance with the composition of the present invention may be replaced by said nucleotide analogs and/or derivatives as long as the modified oligonucleotides remain functionally equivalent to their unmodified counterparts, i.e. as long as they maintain essentially the same portfolio of biological activities that are described in accordance with this invention. "Essentially the same portfolio of biological activities" means that the modified oligonucleotides described above display at least one of the biological activities described in accordance with this invention. Alternatively or additionally, the different biological activities of the modified oligonucleotides may be more or less pronounced compared to the corresponding activities of their unmodified counterparts. [Emphasis added.]

As should be clear from the passage reproduced above, the term "nucleotide analog or derivative" does not refer to a backbone modification. Rather, backbone modifications are the subject of current claims 109-110.

Further in conjunction with the above definitions, the recitation "a *corresponding* nucleotide analog or derivative" in claim 107 makes clear to those skilled in the art that a claimed analog or derivative of a particular nucleotide would not substitute, for example, a pyrimidine-containing nucleotide for a purine-containing nucleotide, or vice versa. For example, a cytidine nucleotide (C) would not replace a guanosine nucleotide (G) to create a new CG dinucleotide, as suggested by the examiner, since such replacement would not constitute replacement by a *corresponding* nucleotide analog. Such an interpretation is fully consistent with the limitation in claim 104, from which claims 107 and 108 depend, that the oligonucleotide does not comprise a CG dinucleotide.

In view of the above, Applicant respectfully submits that claims 107 and 108 are expressed in proper dependent form and accordingly requests that the objections to claims 107 and 108 be withdrawn.

Claim Rejections – 35 U.S.C. § 112, First Paragraph

Claims 104-110 and 112-114 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The examiner states on page 3 of the Office Action that the

specification, while enabling for a method of increasing antigenicity to a tumor in a subject having a tumor comprising administering a tumor-specific antigen and an adjuvant, wherein the adjuvant is an oligonucleotide 10-50 nucleotides long comprising a sequence chosen from GGGGG, GAGGG, GGGAG, GTGGG, GGGTG, wherein the oligonucleotide does not comprise a CG dinucleotide, does not reasonably provide enablement for a method of treating a tumor in a subject. On page 5 of the Office Action the examiner states that the specification enables the skilled artisan to use the claimed method for increasing antigenicity of tumor cells in a subject to a tumor specific antigen.

Applicant respectfully disagrees with the examiner's assertion that undue experimentation is required for one of ordinary skill in the art to use the claimed invention, for the following reasons.

Although demonstration of a working example is not a statutory requirement, working examples are provided in the specification, including those with in vivo models, as acknowledged by the examiner. The working examples provided disclose such parameters as effective dosage and the mode of administration, so as to enable one of skill in the art to use the invention. Consequently, one of ordinary skill in the art using the invention is not burdened with undue experimentation beyond routine optimization for specific use.

Applicant respectfully disagrees with the examiner's characterization of the experimental results presented herein as "unpredictable". The fact that the embodiments of the invention did not produce positive results in every assay tested does not mean that they are unpredictable, because both positive data and negative data are *consistent and statistically reliable*. In fact, the fact that G-motif ODN prevent lethal shock induced by immunostimulatory DNA (Example 5) but not superantigen- or LPS-induced lethal cytokine syndrome (Example 6), demonstrates the specificity of the mechanism of its action. These examples provide further guidance as to how the invention is to be utilized.

The examiner states on page 4 of the Office Action that "the effectiveness of using tumor specific antigens for treating cancer in a patient is considered unpredictable." Applicant respectfully disagrees. Applicant asserts that at the time of filing of the present application, it

was recognized in the art that specifically targeting tumor-specific antigens present in a subject constituted a potential means of cancer treatment. General appreciation for such concept in the art is evidenced by, for example, the fact that an entire chapter from the 1997 textbook Cellular and Molecular Immunology, 3rd Ed. (Abbas et al., Chapter 18 "Immunity to Tumors", W.B. Saunders Company, Philadelphia; copy provided as Exhibit A) is devoted to the topics of tumor antigens, immunity to tumors, tumorigenesis, and immunotherapy of tumors. In addition, a number of publications were published exploiting such an approach as cancer immunotherapy. For example, Tanaka et al. in an article published in 1997 (*Cancer Res.*, 57:4465-68; copy provided as Exhibit B), reported the successful induction of antitumor cytotoxic T lymphocytes with a MAGE-3-encoded synthetic peptide presented in the context of human leukocyte antigen (HLA)-A24. Subsequently, Nishiyama et al. (*Clin. Cancer Res.*, 7:23-31 (2001) ; copy provided as Exhibit C) demonstrated, in a clinical study, that autologous dendritic cells pulsed with the same HLA-A24-specific MAGE-3 peptide was effective in significantly reducing the size of lymph node metastasis and/or liver metastasis in patients.

As the examiner recognizes and concurs (page 3, 1st paragraph of the Office Action), the invention discloses adequate examples for "enabling for a method of increasing the antigenicity to a tumor in a subject having a tumor, comprising administering a tumor-specific antigen and an adjuvant". Therefore, one of ordinary skill in the art at the time of the filling of the instant application would have no trouble appreciating that the observed increase in antigenicity is directly relevant to the ability of immune cells to attack tumor cells, i.e., treating the tumor.

For example, on page 4 of the Office Action the examiner notes that Example 7 indicates that G motif ODN act as adjuvants for generation of antigen-specific cytotoxic T cells in vivo. As is well known by those skilled in the art, cytotoxic T cells (CTLs) are important effector cells in tumor immunity, i.e., for killing of tumor cells. Indeed, Abbas et al. (cited above) teaches that CTLs provide effective anti-tumor immunity *in vivo* (p. 396).

Also on page 4 of the Office Action the examiner notes that Example 8 displays that G-motif (ODN PZ2) induced NK activity in vivo in experimental mice. As is well known by those skilled in the art, natural killer (NK) cells are important effector cells in tumor immunity, i.e., for

killing of tumor cells. Indeed, Abbas et al. (cited above) teaches that NK cells, including IL-2-activated NK cells, kill many types of cells, including tumor cells. In addition, Abbas et al. teaches that down-regulation of MHC expression on many tumor cells, which may allow them to escape CTL lysis, makes them particularly good targets for NK cells (p. 396).

On page 5 of the Office Action the examiner states that the prior art does not provide "a correlation or nexus between the obtained studies such as those provided by the applicant with results the skilled artisan would reasonably expect to see for treating a tumor in a vertebrate subject using the claimed method". The examiner cites Leitner et al., *Current Pharmaceutical Design* (2001) 7:1641-67, in support of this assertion. The reference by Leitner et al., however, is directed to entirely different subject matter from that of the instantly claimed invention. In particular, Leitner et al. discusses DNA and RNA vaccination (wherein the nucleic acid encodes the antigen) and CpG DNA as an adjuvant. As noted above, the claimed subject matter expressly excludes CpG DNA. Reference to Leitner et al. thus appears to be inapposite. Accordingly, Leitner et al. cannot support the examiner's assertion.

From the above it should be clear that one skilled in the art could, contrary to the assertion by the examiner, make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. Accordingly Applicant respectfully submits that the invention is adequately enabled and respectfully requests that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

Claim 114 is rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The examiner points out that the phrase, "represents the 3' terminus of the oligonucleotide" recited in claim 114 is a relative term which renders the claim indefinite.

Upon careful review of the examiner's remarks, it is unclear to Applicant what the examiner finds to be indefinite. Claim 114, in view of claim 104 from which it depends, clearly

defines limitations of oligonucleotides. First, the size of the oligonucleotide is defined to be 10-50 nucleotides long (claim 104). Second, the composition of the oligonucleotide is also defined to comprise a sequence selected from GGGGG, GAGGG, GGGAG, GTGGG and GGGTG, and not to comprise a CG dinucleotide (claim 104). Claim 114 adds the further limitation that the sequence (which is selected from GGGGG, GAGGG, GGGAG, GTGGG and GGGTG) is at the 3' terminus of the oligonucleotide, defining the exact location of the motif within the oligonucleotide. Since every limitation is specific and defined, Applicant cannot identify a component that is "relative" or "indefinite" as asserted by the examiner. Accordingly, Applicant respectfully traverses the rejection and asks that the examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, second paragraph.

Claim Rejections – 35 U.S.C. § 102

Claims 107 and 108 are rejected under 35 U.S.C. § 102(e) as being anticipated by Krieg et al. (U.S. Patent 6,339,068). Krieg et al. teaches CG dinucleotide-containing nucleic acid molecules. The rejection is based on the assumption by the examiner that claims 107 and 108 are improper because, as discussed above, the limitations of said claims would allow for the introduction or inclusion of a CG dinucleotide, where CG dinucleotide-containing oligonucleotides are disclosed in the cited reference. Applicant respectfully traverses, for reasons set forth above. More specifically, by reciting "a *corresponding* nucleotide analog or derivative" in claims 107 and 108 and in view of the disclaimer that the oligonucleotide does not comprise a CG dinucleotide, the claimed invention clearly avoids the cited reference. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 102(e) be withdrawn.

Claims 107 and 108 are also rejected under U.S.C. 35 § 102(a) as being anticipated by Wagner et al. (WO 98/32462). Wagner et al. teaches CG dinucleotide-containing nucleic acid molecules. For the same reason provided above, the teachings claimed in claims 107 and 108 are not anticipated by the cited reference. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 102(a) be withdrawn.

Summary

Arguments are presented herein to overcome the objection and all the rejections. In view of the foregoing remarks, this application should now be in condition for allowance. Applicant respectfully requests a favorable response. The examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the matter in condition for allowance.

Respectfully submitted,

Hermann Wagner et al., Applicant

By: Alan W. Steele
Reg. No. 45,128
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, MA 02210
Tel. (617) 646-8000

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